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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/616,622	07/14/2000	Kristoffer Hellstrand	MAXIM.078A	6563

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EXAMINER
EWOLDT, GERALD R

ART UNIT	PAPER NUMBER
1644	

DATE MAILED: 11/20/2001

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/616,622	Applicant(s) Hellstrand et al.
	Examiner G.R. Ewoldt	Art Unit 1644

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☒ Responsive to communication(s) filed on *Sep 4, 2001*.

2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) *1-34* is/are pending in the application.

4a) Of the above, claim(s) *2-7 and 14-34* is/are withdrawn from consideration.

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) *1 and 8-13* is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9) ☐ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are a) ☐ accepted or b) ☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a) ☐ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☒ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

a) ☐ The translation of the foreign language provisional application has been received.

15) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s). _____
4) ☐ Interview Summary (PTO-413) Paper No(s). _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

1. Applicant's election without traverse of Group V, Claims 1 and 8-13, in Paper No. 9, filed 9/04/01, and the specific ROM inhibitor histamine, is acknowledged.

2. Claims 2-7 and 14-34 are withdrawn from further consideration by the examiner, 37 C.F.R. § 1.142(b) as being drawn to nonelected inventions.

3. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4. Claims 1 and 8-13 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. Specifically, the specification provides insufficient evidence that the claimed method would function for activating cytotoxic lymphocytes or for protecting cytotoxic lymphocytes after administering diphenylionodonium (DPI)to a patient.

The method of the instant claims comprises activating and protecting cytotoxic lymphocytes by administering to a patient a composition comprising DPI and histamine. It is well known in the art that histamine can protect certain cytotoxic lymphocytes from monocyte-induced apoptosis *in vitro*, i.e., protect NK cells in the presence of monocytes (see, for example, Hellstrand et al., 1995, IDS). However, neither the instant specification, nor the prior art teach that either histamine or DPI can activate cytotoxic lymphocytes. Indeed, the prior art teaches that DPI is actually immunosuppressive. See, for example, Kalsi et al. (1993) which teaches that "DPI exert(s) potent suppressive effects on human lymphocyte proliferation." Given that the prior art teaches an effect essentially opposite that of the instant claims, a method reciting said activation would require some enabling demonstration, i.e., a working example. The instant application provides just a single relevant working example (Example 2). Said example discloses that DPI can "protect" NK cells from monocyte induced apoptosis, however, said example

provides no demonstration that said NK cells are activated by DPI. It is noted that the cells of Example 2 were cultured in 100 U/ml of IL-2; it is a well-known fact that IL-2 is an activator of cytotoxic lymphocytes. As such, the "activation" of cytotoxic lymphocytes by DPI must be considered highly unpredictable. Said unpredictability would require undue experimentation.

Regarding the specific claim to "activating" and "protecting" cytotoxic lymphocytes comprising "administering to the patient," said method comprises an *in vivo* method of treatment. *In vivo* methods are considered highly unpredictable and mere assertion of the efficacy of an *in vivo* method of treatment is not considered enabling. As the specification discloses no *in vivo* examples, the method of the instant claims is considered to require undue experimentation.

It is also noted that Claim 13 recites the inhibition of the production of the specific ROM hydrogen peroxide. However, it is also noted that no specific assay of the inhibition of hydrogen peroxide production is disclosed. As such, the claim comprises only an assertion of a possible mechanism by which the highly unpredictable method of the instant claims might function. Thus, said mechanism is also highly unpredictable, and given said unpredictability, said mechanism would also require undue experimentation.

In re Wands, 858 F.2d at 737, 8 USPQ2d at 1404 (Fed. Cir. 1988) indicates that the more unpredictable an area is, the more specific enablement is necessary in order to satisfy the statute. Thus, in view of the quantity of experimentation necessary, the lack of sufficient working examples, the unpredictability of the art, and the lack of sufficient guidance in the specification, it would take undue trials and errors to practice the claimed invention.

5. Claims 1 and 8-13 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor, at the time the application was filed, had possession of the claimed invention.

There is insufficient written description to show that Applicant was in possession of a "cytotoxic lymphocyte" other than an NK or cytotoxic T cell.

The claimed method comprises a method of activating or protecting cytotoxic lymphocytes. As such, an adequate description of said cytotoxic lymphocytes comprises a critical element of instant claims. The specification, however, discloses that cytotoxic lymphocytes include not just NK and T cells, but also "non-cytotoxic cells such as T-helper cells that assist in the activation of a lymphocyte with cytotoxic capabilities." Thus, the claims are clearly drawn to a broad genus comprising an unknown and undescribed number of species. Given the disclosure of just a single non-cytotoxic cell species, and further, that said species (T helper cells) is not generally considered in the immunological arts to be encompassed by the term "cytotoxic lymphocytes", one of skill in the art would conclude that the specification fails to disclose a representative number of species to describe the claimed genus. See *Eli Lilly*, 119 F.3d 1559, 43 USPQ2d 1398.

6. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

7. Claims 1 and 8-13 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Specifically:

A) the use of the compound name "diphenylionodonium" in Claim 1 renders the claim vague and indefinite as no such compound is known to exist, as evidenced by the fact that no compound with said name has not been found in either the Kirk-Othmer Encyclopedia of Chemical Technology or the Sigma Chemical Company catalog,

B) the recitation of "the patient" in Claim 1 has no antecedent basis in the claim,

C) the recitation of "said effective amount" in Claims 9 and 10 renders the claims vague and indefinite as it is unclear whether "said effective amount" refers to the amount of DPI or the amount of ROM inhibitor,

D) the recitation of "said cytotoxic lymphocyte stimulatory composition" in Claims 11 and 12 has no antecedent basis in Claim 1.

8. No claim is allowed.

9. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Dr. Gerald Ewoldt whose telephone number is (703) 308-9805. The examiner can normally be reached Monday through Thursday and alternate Fridays from 7:30 am to 5:30 pm. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (703) 308-3973.

Papers related to this application may be submitted to Technology Center 1600 by facsimile transmission. Papers should be faxed to Technology Center 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center telephone number is (703) 305-3014.

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November 14, 2001